Osteoarthritis and Cartilage (1999) **7,** 351–352
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Article No. joca.1998.0195, available online at http://www.idealibrary.com on IDEAL
1063–4584/99/030351+02 $12.00/0

Osteoarthritis and Cartilage
Journal of the OsteoArthritis Research Society International

Is there preliminary in-vivo evidence for an influence of nonsteroidal antiinflammatory drugs on progression in osteoarthritis? Part II—evidence from animal models

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Since Hoffman synthesized aspirin (ASA), more than 100 years ago, there is a general agreement that nonsteroidal antiinflammatory drugs (NSAIDs) provide symptomatic relief for millions of people with osteoarthritis (OA). The role of NSAIDs became confused with the discovery that some R-enantiomers of the profenic group of NSAIDs were as effective as S-series enantiomers in relieving pain in OA. This was despite the fact that the R-enantiomeres were several hundred fold less active in inhibiting prostaglandin (PG) synthesis and ineffective in animal models of inflammation.

The value of NSAIDs in OA became further confused with the frequency of adverse reactions (particularly in the elderly) and reports of rapid destructive arthropathy in patients taking high doses of indomethacin. Consequently, Brandt (1993) published a sharp review with an intriguing title: 'Should OA be treated with NSAID?'

We do not yet fully understand the etiopathogenesis of OA and the mechanism of NSAIDs activity on the intrinsic and migrating cells of the joint. What is known is controversial and filled with personal opinions. Animal models have been of some help in defining these processes.

If we are to assume that NSAIDs are effective in providing symptomatic relief and that NSAIDs have analgesic as well as anti-inflammatory properties, we can pose the following questions: (1) what is the evidence that OA is an inflammatory joint disease and (2) what is the evidence that the joint pain in OA is due to synovitis?

Inflammation

We know the histology of early and advanced OA and that the correlation between histologic evidence of synovitis and cartilage damage is inconsistent. Evidence exists that macrophage or autocrine chondrocyte produced cytokines, like interleukin (IL)-1 and tumor necrosis factor (TNF)-α, can accelerate the breakdown of articular cartilage. Through the interleukin 1 receptor (IL-1R) and the tumor necrosis factor alpha receptor (TNF-αR), cytokines precipitate the inducible enzymes nitric oxide (NOS)-2 and cyclooxygenase (COX)-2. Through these mechanisms, NSAIDs can be useful by reducing cytokine production, toxic oxygen free radicals, noxious prostaglandins, leukotriene synthesis, etc.

However, the biochemical and metabolic changes of OA in the articular cartilage of anterior cruciate deficient (ACLT) canines appear independent of the presence of synovitis. Treatment with prednisone, low enough to not inhibit PG synthesis by chondrocytes but high enough to inhibit IL-1 production, had no effects on the development of OA in the model. Moreover the indiscriminate blockage of PG production reduce the presence of PGE-2 which normally has a stimulating activity, via adenyl cyclase, on uridine diphosphate-glucose deydrogenase and glutamine-fructose-6-phosphate aminotransferase—enzymes employed in the synthesis of hexuronic acid and chondroitin sulfate.

PGE-2 also has a feedback effect in reducing the production of IL-1 by macrophages and in IL-1R expression on chondrocytes. PG analogues administered with NSAIDs have been shown to diminish the deleterious effects of NSAIDs on cartilage.

Is there evidence for a direct effect of NSAIDs on articular cartilage metabolism?

From observations in animal models of OA, there is a different response of cartilage to different NSAIDs: (1) OA was markedly accelerated in C57Black mice, who develop a spontaneous OA; (2) dogs fed with ASA had significantly lower

concentration of proteoglycans in the cartilage matrix; (3) water content was increased by naproxen in ACLT canines; (4) depletion of matrix proteoglycans with increased degeneration of cartilage chondrocytes from the effects of NSAIDs.

However, some NSAIDs show a favorable effect on OA articular cartilage – although there are differing results in different models: (1) in a study of proteoglycan metabolism of cartilage explants, Palmosky *et al.* showed different effects of different NSAIDs; (2) pirprofen significantly reduced cartilage breakdown severity in rabbits; (3) tiaprofenic acid reduced the size of ulcers on femoral condyles and tibia plateaus and produced less marked histological changes in ACLT dogs; (4) tiaprofenic acid showed a chondroprotective action in the ACLT canine model; and (5) tiaprofenic acid in a prophylactic treatment, prevented OA progression in the ACLT canine model.

There is less controversy on the effects of NSAIDs on catabolism: (1) NSAIDs are credited on having some favorable effects on the cartilage metabolism in controlling degradation of cartilage matrix; (2) in relation to inhibition of proteinases, tenoxicam and indomethacin have opposite effect on the activation of stromelisin; (3) etodolac administered as 'prophylactic' in a rabbit experimental OA, partly prevented cartilage disruption; (4) piroxicam decreased fibrinolytic activity by increasing plasminogen activator inhibitor (PAI) activity and decreasing urokinase-plasminogen activator (u-PA) release. this favors the surface clearance of urokinase-plasminogen activator receptor (u-PAR) *in vitro* and *in vivo*.

Plasminogen activator

Our laboratory has been interested in the u-PA cascade and its relation to articular cartilage breakdown. Resident articular cells secrete PAs and PAIs, and express u-PAR on their membrane [1, 2]. Data indicate that synthesis and release of u-PA and PAI-1 by both chondrocytes and synoviocytes are under the control of a variety of cytokines and grow-factors found in the diseased joints. Secretion of u-PA is followed by autocrine and paracrine binding to cell surface u-PAR, which concentrates the u-PA activity at the cytoplasmic membrane.

Receptor-bound u-PA activates a multi-enzyme cascade by operating a cleavage on plasminogen, which is transformed into serine-protease plasmin. Plasmin degrades directly or indirectly, through activation of pro-matrix metalloproteinase (MMP), the greatest part of extracellular matrix molecules. Data indicate that the activation of pro-MMPs results from the upstream interaction of u-PA and u-PAR and the following activation of proteolytic cascades [3].

Our hypothesis is that upstream inhibition of u-PAR is mandatory to control all the mechanisms which involved in cell invasion, matrix degradation, neo-angiogenesis, and cell growth. These are strict requirements for resident articular cells that mediate inflammatory and degenerative joint pathologies. To demonstrate this we used the antisense oligonucleotide tecnology to control the expression of u-PAR in synoviocytes and chondrocytes: the blockade of u-PAR expression results in impairment of all the u-PA/uPAR-dependent events.

As previously published, many NSAIDs can control and reduce, in different ways and grades, the u-PA production and u-PAR expression on the surface of chondrocytes and synoviocytes, accounting so of a reduced activity on cartilage breakdown [1, 2].

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